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Application of astatine-210: Evaluation of astatine distribution and effect of pre-injected iodide in whole body of normal rats

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HIGHLIGHTS

- Free ^{210}At was administered to normal rats instead of free ^{211}At.
- The pre-injection of I- reduced the accumulation of ^{210}At in the thyroid and stomach.
- We estimated the behavior of ^{211}At based on the biodistribution of ^{210}At.

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ABSTRACT

We proposed use of astatine-210 in preclinical study. Astatine-210 has higher yield of production and is easier to quantify than astatine-211. We produced astatine-210 with Bi target and 40 MeV alpha beam accelerated by cyclotron, free astatine-210 was separated and injected to normal rats. Three male rats (blocking group) were injected non-radioactive iodide before injection of astatine-210. Compared with the control group, the astatine-210 accumulations in the blocking group decreased to 24% in the thyroid.

1. Introduction

Recently, much attention has been paid to targeted α-particle therapy (TAT). Because of the shorter range and higher linear energy transfer (LET) of α-particles, targeted small cell clusters can be irradiated more effectively using α-particles, compared with β-particles (Hada and Georgakilas, 2008; Kruijff et al., 2015; Lassmann et al., 2002). Thus, TAT is expected to enable a strong effect localized within a small range. In 2013, radium-223 (^{223}Ra) has been approved by the European Medicines Agency the U. S. Food and Drug Administration as the first α-therapy for the treatment of symptomatic metastatic castration-resistant prostate cancer (Kluetz et al., 2014). Also in Japan, ^{223}Ra has also been approved by the Pharmaceuticals and Medical Devices Agency (2016). Other nuclides expected to be useful for TAT include terbium-149 (^{149}Tb), lead-212/bismuth-212 (^{212}Pb/^{212}Bi), bismuth-212 and 213 (^{212,213}Bi), astatine-211 (^{211}At), actinium-225 (^{225}Ac) and thorium-227 (^{227}Th) (Guérard et al., 2013; Thorp-Greenwood and Coogan, 2011).

^{211}At is known as a halogen element (Group 17) (Champion et al., 2010). The chemical properties of astatine are similar to iodine (Wilbur, 2013). Therefore, examples of astatine-labeled compounds can be synthesized in a manner similar to that used for iodine. For example, the synthesis of *m*-[^{211}At]astatobenzylguanidine, an analogue of *m*-iodobenzylguanidine, is based on astatination at aromatic rings (Boyd et al., 2004; Strickland et al., 1995; Vaidyanathan and Zalutsky, 1992; Vaidyanathan et al., 1997). This technique is also used for antibody labeling (Hadley et al., 1991; Lindegren et al., 2008).

The basic properties of astatine must be well understood before the clinical application of ^{211}At. The degradation of ^{211}At-labeled antibodies and the subsequent accumulation of free ^{211}At in the thyroid gland have been problematic for clinical studies (Andersson et al., 2009). Larsen et al. intraperitoneally administered a large amount of potassium iodide (165 mg/kg) to mice before administration of ^{211}At and showed that the accumulation of ^{211}At was blocked for 4 h (Larsen

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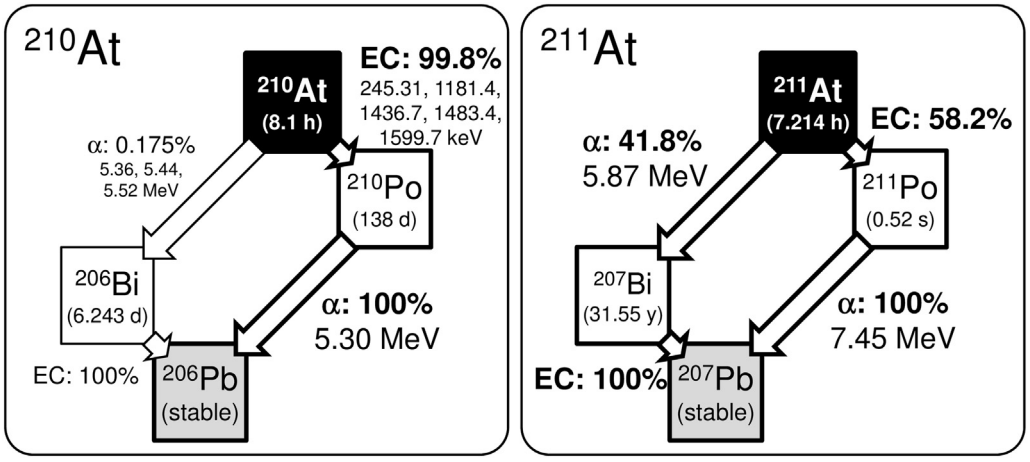

Fig. 1. Decay properties of ^{211}At, ^{210}At, and their daughters.

et al., 1998). However, they did not evaluate the blocking effect at 4 h after the administration of ^{211}At. Spetz et al. injected free ^{211}At to normal rats (Spetz et al., 2013). In their work, the biodistribution and dosimetry of free ^{211}At were evaluated, and ^{211}At accumulation peaked in the thyroid glands of normal rats at 18–24 h after ^{211}At injection. However, they did not perform a blocking study using iodine. Accumulation of ^{211}At damages the normal thyroid gland. Pre-injection of non-radioactive iodide is considered effective for protecting the thyroid. The dose of blocking agent was determined referring the ^{131}I-MIBG study. (Quach et al., 2011; van Santen et al., 2002) In the clinical case of ^{131}I-MIBG, 6 mg/kg of potassium iodide was administered. In our study, the dose was set at 10 mg/kg so that it can be sufficiently blocked. In many cases, potassium iodide is selected for iodide blocking, however the same effect can be expected with sodium iodide. In this study, to sufficiently protect the thyroid gland, the blocking agent was NaI, and its dose was 10 mg/kg. This amount of sodium iodide corresponds to 11 mg/kg of potassium iodide in based on amount of iodide anion.

In this paper, we proposed the use of astatine-210 (^{210}At), rather than ^{211}At, in a preclinical study. ^{210}At and ^{211}At have the same chemical properties and similar half-lives (8.1 ± 0.4 h and 7.214 ± 0.007 h, respectively). As shown in Fig. 1, ^{210}At mainly emits photons (γ-rays) and ^{211}At mainly emits α-rays (Ryan, 1998). The energies of γ-rays emitted from ^{210}At are 245, 1181, 1437, 1483 and 1600 keV. Using the 245 keV γ-ray, absolute quantification can be easily performed using a high-purity germanium detector (HPGD) or gamma counter, while the quantification of ^{211}At is more difficult because of the need to measure low energies (K X-ray from ^{211}Po) emitted by ^{211}At or to perform α-spectrometry. ^{210}At has a higher production yield than ^{211}At. The cross-section peaks of ^{209}Bi(α, 2 n)^{211}At and ^{209}Bi(α, 3 n)^{210}At reactions are about 900 mb (31 MeV) and 1200 mb (38 MeV), respectively (Fig. 2) (Hermanne et al., 2005; Kelly and Segrè, 1949; Lambrecht and Mirzadeh, 1985; Stickler and Hofstetter, 1974). In addition, air concentration limits based on ICRP Publication 68 and 72 of ^{211}At (2×10^{-4} Bq/cm^3) is more severe than ^{210}At (4×10^{-3} Bq/cm^3) (Kawai and Endo, 2000; Kawai et al., 2000). Therefore, more concerns are needed to use ^{211}At than ^{210}At.

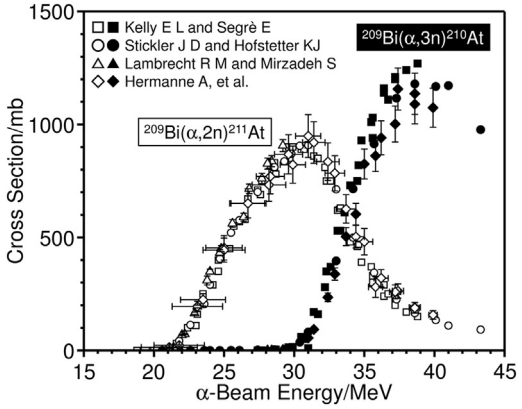

Fig. 2. Cross section of ^{209}Bi(α,2n)^{211}At and ^{209}Bi(α,3n)^{210}At reactions (Hermanne et al., 2005; Kelly and Segrè, 1949; Lambrecht and Mirzadeh, 1985; Stickler and Hofstetter, 1974).

In the present work, we produced ^{210}At by accelerator, and prepared ^{210}At solution for injection by solvent extraction. As one application of ^{210}At, we investigated the biodistribution of ^{210}At in normal rats about 1 day (23 ± 1 h) after the injection of ^{210}At as well as the effect of iodide blocking.

2. Materials and methods

2.1. Preparation of ^{210}At

^{210}At was produced in an AVF cyclotron at the Research Center for Nuclear Physics (RCNP), Osaka University. A 25-μm Bi foil (The Nilaco Corporation) was covered with a 10-μm aluminum foil and used as the target. The target was then irradiated with an α-beam (40 MeV, 250 pnA) for 2 h. The main nuclear reaction was ^{209}Bi(α,3n)^{210}At. After the irradiation, the Bi foil was allowed to cool for about 2 h.

The chemical separation was performed in a manner similar to that reported previously (Visser and Diemer, 1983). The irradiated Bi foil was dissolved in 2.5 mL of 5 mol/L nitric acid. This solution was then mixed to dissolve the Bi foil completely. The entire Bi solution was transferred to a 15-mL centrifuge tube and 4 mL of carbon tetrachloride (CCl_4) was added; the tube was then shaken for a few minutes. The solutions were leaved for 5–10 min until the two phases were completely separated. The organic phase was separated and transferred to another centrifuge tube. Then, 0.5 mL of 2 mol/L NaOH solution was added to this tube for a back extraction. After the back extraction, the aqueous phase was separated and neutralized to pH 6 by adding a small amount of hydrochloric acid. The total volume of the product solution was 0.7 mL. 100 μL of this product solution was taken as "^{210}At standard source".

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